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Non-invasive tests for MetALD and alcohol-related liver disease ☆

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Summary

Metabolic- and alcohol-related liver disease (MetALD) and alcohol-related liver disease (ALD) are major drivers of the global burden of cirrhosis. While metabolic dysfunction-associated steatotic liver disease (MASLD) affects nearly one-third of the global population, ALD and MetALD, though far less common, account for a disproportionately high rate of liver-related complications and deaths. Despite this, research and clinical focus on ALD and MetALD remain limited. A critical barrier is the late stage at which these conditions are typically diagnosed, often after the onset of decompensation. In this review, we explore the potential of non-invasive tests (NITs) to change the diagnostic landscape of ALD and MetALD. NITs offer a practical and scalable means to detect liver disease at earlier, compensated stages, before symptoms emerge, thereby opening a window for timely intervention. Beyond diagnosis, these tools also serve important roles in risk assessment, disease monitoring, and evaluating treatment response. As interest in therapeutic developments for ALD and MetALD grows, NITs are expected to become central to trial design, helping to identify suitable participants, assess ongoing alcohol use, and monitor efficacy without reliance on invasive biopsies. We also discuss broader strategies necessary to support early detection, including policy changes, stigma reduction, and improved access to care. Finally, we consider emerging biomarkers and their promise in advancing precision medicine approaches tailored to this high-risk patient population.

Introduction and clinical needs

Alcohol-related liver disease (ALD) and metabolic- and alcohol-related liver disease (MetALD) account for an estimated 20 million cases of compensated cirrhosis worldwide, leading to over 330,000 cirrhosis deaths annually.[1] Along with metabolic dysfunction-associated steatotic liver disease (MASLD), these conditions represent the most common causes of steatotic liver disease (SLD).[2] MASLD is defined as the presence of hepatic steatosis, with at least one cardiometabolic risk factor, and a self-reported alcohol intake below 20 g/day for women and 30 g/day for men. In contrast, ALD is defined by alcohol intake exceeding 50 g/day for women and 60 g/day for men. MetALD refers to the common scenario in which a patient with MASLD consumes alcohol above MASLD thresholds but still below those defining ALD.[2] The umbrella term of SLD is characterised by a "burden paradox" between its high prevalence and the relatively low risk of liver-related events in certain subclassifications.[3] The disease prevalence for MASLD is estimated at 31-34%, whereas MetALD and ALD are less common, with prevalence rates of 2-8% and 1-4%, respectively.[4–9] Despite their lower prevalence, MetALD and ALD are associated with a markedly higher risk of liver-related events and mortality (approximately 45%), compared to MASLD (an estimated 4%).[3,10,11] Despite this high morbidity and mortality, the ALD research field is largely overlooked and underprioritised.[7,12–14]

In recent years, the importance of early detection of liver disease has been increasingly recognised.[15] This is especially urgent for ALD and MetALD where patients are rarely diagnosed at early stages.[16] Shifting from late diagnosis to early detection is a complex task that will need to be tackled from multiple angles simultaneously (Fig. 1). Essential strategies include policy measures, raising awareness, structural changes to reduce stigma, and addressing health inequalities. These efforts aim to shift from a passive approach – where symptom development and decompensation prompt diagnostic investigations – to an active approach utilising non-invasive tests (NITs) to detect compensated liver disease before symptom onset, enabling early treatment and prevention of disease progression.[15,17,18] On top of this, the use of NITs is essential for case finding and risk stratification.[19] Non-invasive strategies for the replacement of liver biopsy are of increasing importance both in clinical practice and in drug development.[20,21]

In this review, we examine current knowledge on the use of NITs for the diagnosis and prognostication of ALD and MetALD, as well as emerging data on tools for monitoring disease progression. Additionally, with more drug trials in ALD on the horizon and with the possibility of a new era of industry-sponsored trials, there is an unmet need for NITs to track treatment response and assess alcohol consumption.[22,23] In this review, we will further outline the potential of NITs in drug

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Keypoints

- Non-invasive tests are available and validated as first-line assessments in the clinical care of patients at risk of MetALD and ALD.
- Non-invasive tests should be applied to shift the paradigm from late diagnosis to early detection.
- Management of patients with MetALD and ALD should follow a holistic approach due to their increased risk of cardiovascular diseases and cancer.
- With emerging drug trials in patients with alcohol-related liver fibrosis and cirrhosis, there is an unmet need for non-invasive tests to monitor treatment response and assess alcohol consumption.

trials and take a look at the future of novel biomarkers for precision medicine.

Diagnostic tests for non-invasive assessment of MetALD and ALD

The first step in assessing patients for SLD is a combined assessment that considers alcohol history, clinical features, biochemistry, and imaging, with histology required only when the diagnosis remains uncertain. An estimate of the degree of fibrosis or presence of cirrhosis is vital as this is the most important indicator of prognosis.[24] Early detection and timely diagnosis of ALD and MetALD are pivotal for reducing mortality by promoting a reduction in alcohol intake or abstinence, monitoring the disease and treating associated cardiometabolic risk factors.[15]

Screening and referral pathways

Most asymptomatic patients with liver fibrosis due to ALD/MetALD are seen in primary care and are likely unaware of their risk. This makes primary care crucial for early detection. Yet, more than 90% of patients who later develop decompensated cirrhosis have been in contact with the healthcare system years before symptomatic liver disease, often with alcohol-related health issues.[25–27] Such contacts represent an opportunity for case finding.

Some NITs like the fibrosis-4 (FIB-4) index, LiverRisk score, or LiverPRO are simple, inexpensive, and applicable to large population groups, making them an attractive option as screening tools in selected at-risk groups.[28,29] Whether liver fibrosis screening is beneficial and cost effective is unknown, as randomised controlled trials evaluating the effect of screening on liver-related events and mortality are lacking.[30,31] However, some data suggest that screening or early detection of ALD with NITs is highly cost effective.[32,33] A Danish study modelled the effects of screening and found that, in a low-prevalence primary care population, the most cost-effective strategy was to refer excess drinkers for an enhanced liver fibrosis (ELF) test, followed by referral to secondary care for liver stiffness measurement (LSM) if the ELF score was positive (>10.5).[32] Assuming either temporary or permanent reductions in alcohol intake after diagnosis, this approach resulted in an incremental cost per QALY (quality-adjusted life year) gained of $5,387 to $8,430.[32] Another study evaluated the use of LSM alone as a screening tool in more than 6,000 primary care patients across Europe and Asia.[33] In a subpopulation of patients at risk of ALD,

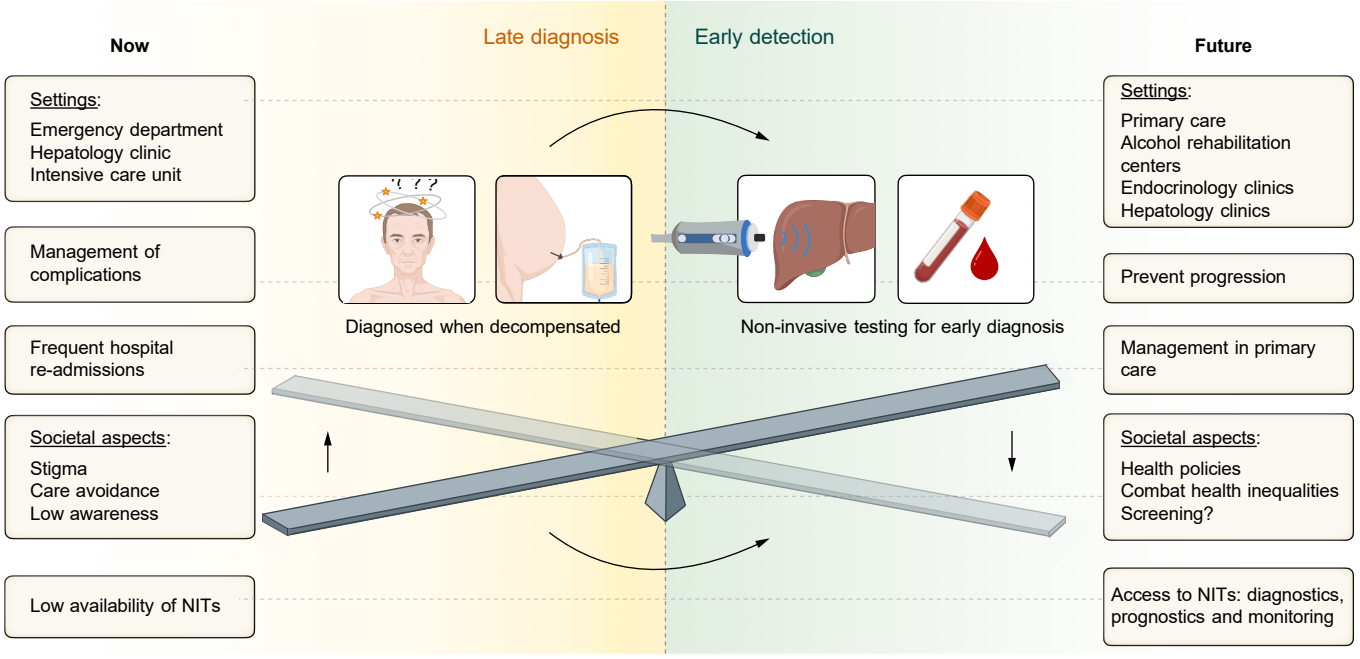

Fig. 1. Shifting the paradigm from late diagnosis to early detection and prevention.

screening was considered cost effective, with a mean incremental cost-effectiveness ratio of €2,570 per QALY.[33]

Interestingly, just participating in screening for liver disease may promote lifestyle changes.[34] In a cohort of 1,850 individuals at risk of ALD, the percentage of people with self-reported excessive drinking had dropped from 46% to 32% six months after participating in the screening study, with a positive screening test being a predictor of decreased intake.[35] Furthermore, a randomised controlled trial performed in community alcohol services indicated that patients with knowledge of their liver stiffness as part of alcohol rehabilitation were more likely to reduce or stop alcohol consumption.[36]

Identifying the right patients in primary care and the link to hepatology clinics is crucial. A retrospective study covering the referral patterns for suspected ALD found that 64% of referrals were unnecessary, as there was no evidence of advanced fibrosis after further investigation. Using FIB-4 ≥1.45 for risk stratification improved the selection of patients for timely referrals, but with a false negative rate of 22%.[37] The EASL NIT clinical practice guidelines recommend FIB-4 as a first-line test in patients at risk of ALD, and if positive (FIB-4 ≥1.3), an LSM by transient elastography (TE), further combined with a patented serum test like ELF if LSM is ≥8 kPa.[20] In a Danish targeted screening study including 953 patients at risk of ALD or MetALD, a sequential pathway of FIB-4 followed by ELF in indeterminate cases (FIB-4 1.30-2.67) correctly classified 85% of patients, compared to 60% when using FIB-4 only.[38]

Evaluation of liver fibrosis, steatosis and inflammation

Blood-based tests

Blood-based NITs for fibrosis staging are traditionally classified as indirect or direct. Indirect tests are routine biochemical markers that are not surrogates of fibrogenic processes and are often combined into scores like FIB-4, aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio, AST-to-platelet-ratio index (APRI), or FibroTest. These tests are often inexpensive and widely available, but with lower diagnostic performances than the best performing direct fibrosis tests.[20] The LiverRisk score is based on simple parameters (age, sex, fasting glucose, cholesterol, AST, ALT, gamma-glutamyltransferase, platelet count) and was developed using three liver stiffness cut-offs as a reference standard.[29] The LiverRisk score was validated in the UK Biobank, where individuals classified as high risk showed a hazard ratio of 471 for liver-related mortality compared to those in the minimal-risk group. The results were consistent in individuals reporting daily alcohol intake.[29] Also based on standard biochemical markers, LiverPRO was developed in a cohort of patients with alcohol overuse, and was validated across five separate European cohorts spanning both primary and secondary care settings. It currently stands as the only CE-certified digital tool of its kind.[28] Few studies are available testing the diagnostic performance of NITs in a pure MetALD cohort. In a low-prevalence Korean cohort, including 462 patients with MetALD, AUROCs for diagnosing advanced fibrosis (defined as magnetic resonance elastography ≥3.6 kPa) were 0.85 for FIB-4 and NFS (NAFLD fibrosis score).[39]

Direct fibrosis tests, which reflect extracellular matrix turnover, include the ELF test – one of the most extensively validated and used blood-based tests – and N-terminal type III collagen propeptide (PRO-C3), which can be used alone or in combination with age, diabetes and platelet count in the ADAPT algorithm.[40–42] The diagnostic performance of ELF is good, with AUROCs of 0.90-0.92 for detecting advanced fibrosis in patients with ALD from both primary, secondary, and tertiary care settings.[43,44] In a meta-analysis on the diagnostic accuracy of ELF for staging fibrosis across aetiologies, the optimised cut-offs for detecting advanced fibrosis and cirrhosis were higher in ALD compared to other aetiologies, with a numerically higher performance of ELF. However, these results were limited by ALD being the least studied aetiology.[45] PRO-C3 and ADAPT were compared to non-patented NITs in a cohort of 426 patients with ALD, which revealed AUROCs for detecting advanced fibrosis of 0.85 for PRO-C3 and 0.88 for ADAPT.[46] The prevalence of advanced fibrosis influences the performance of diagnostic tests.[20] FIB-4 has been extensively tested as a first-line screening test to rule out advanced fibrosis in low-prevalence populations.[20,38,39,43] In contrast, evidence supporting the use of PRO-C3 and ADAPT is limited, which should be considered when interpreting their performance.[46]

The caspase-cleaved keratin-18 fragments M30 and M65 generated during apoptosis and necrosis have been tested as markers of inflammation. In particular, M30 exhibited good diagnostic accuracy for hepatic inflammatory activity.[47,48]

Imaging

The performance of LSM by TE for diagnosing fibrosis stage in patients with ALD has been assessed in several studies. An individual patient data meta-analysis, including ten studies comprising 1,026 patients with ALD, demonstrated AUROCs of 0.90 and 0.91 for diagnosing advanced fibrosis (≥F3) and cirrhosis.[49] Cut-offs used in the included studies varied greatly and the meta-analysis found an optimised cut-off of 12.1 kPa for detecting advanced fibrosis (≥F3), with a sensitivity of 81% and a specificity of 83%, but in a very high prevalence population.[49] Liver stiffness declines during alcohol withdrawal in patients admitted for detoxification, paralleling reductions in inflammatory markers and supporting a role for alcohol-related steatohepatitis in increasing stiffness.[50,51] To more accurately classify patients using liver stiffness, it is suggested to repeat the measurement after reduced drinking in patients with biochemical evidence of liver inflammation.[20] A pilot study found the ELF test to be stable in the months after alcohol withdrawal.[52] Studies have demonstrated excellent inter-operator agreement for TE, with intraclass correlation coefficients ranging from 0.93 to 0.98.[53,54] However, short-term variability in LSM can still occur due to factors such as hepatic inflammation, recent food intake, or obstructive cholestasis. To reduce measurement variability and ensure consistency across operators, standardised training and strict adherence to quality criteria, such as obtaining at least 10 valid measurements with an interquartile range ≤30% of the median, are essential.[55]

Non-invasive diagnosis of alcohol-related steatosis using the hepatorenal index by B-mode ratio, B-mode ultrasound, and controlled attenuated parameter all showed modest and comparable diagnostic accuracies.[56] Traditionally, the presence of liver steatosis has been viewed as rapidly reversible and a less important predictor of prognosis. However, patients with alcohol-related, biopsy-verified pure steatosis, without

fibrosis, have been shown to have an increased 5-year risk of cirrhosis and mortality.[57]

Holistic approach to management of patients with MetALD and ALD

There is a well-established correlation between population-level alcohol intake and liver-related mortality,[15] but individuals with alcohol use disorder (AUD) also face high risks of numerous extrahepatic somatic and psychiatric diseases compared to the general population.[58] Patients with ALD exhibit increased mortality from cardiovascular diseases, non-hepatic cancer, infections, and dementia, and may suffer a high burden of disease from poor mental health and socioeconomic challenges.[59,60] An epidemiological study on cause-specific mortality in over 23,000 patients with ALD found that in the first 5 years after an ALD diagnosis, liver disease caused nearly half of all deaths. However, beyond 5 years, mortality shifted to predominantly extrahepatic causes.[10] The many preventable causes of morbidity and mortality in patients with ALD call for a holistic approach to management (Fig. 2).

Healthcare professionals can apply five key strategies to ensure comprehensive management of liver-related issues and extrahepatic conditions in patients with MetALD and ALD: screen and monitor for somatic and psychiatric comorbidity; offer integrated care; support overall lifestyle modifications; ensure mental, financial and social support; and provide behavioural and pharmaceutical interventions for AUD.[61]

Effective management starts with regular screening and monitoring for comorbid conditions (Fig. 2). This includes routine laboratory tests, imaging, psychometric, and physiological tests to detect early signs of complications and enable timely intervention.[62] The complex health needs of patients with MetALD and ALD also require a multidisciplinary treatment plan. Integrated care should be coordinated among hepatologists, primary care physicians, social workers, cardiologists, endocrinologists, oncologists, psychiatrists, and addiction specialists.[63] Global lifestyle changes are often essential, as many patients with ALD require nutritional support, physical rehabilitation, and smoking cessation programmes. Access to counselling, support groups, and training programmes is vital to achieve long-term overall improvements in cardiometabolic health and improve health-related quality of life.[63] Addressing mental health and socioeconomic issues is equally critical, as poor mental health, financial insecurity, and lack of social support act as significant barriers to health-seeking behaviour, self-care, and adherence to therapy.[64] Finally, the most important factor to improve survival after a diagnosis of ALD is pharmaceutical or behavioural AUD treatment to induce and maintain long-term sobriety.[65] Combined cognitive-behavioural therapy and anti-craving medication in expert alcohol treatment centres lowers relapse risk and enhances patient survival.[66]

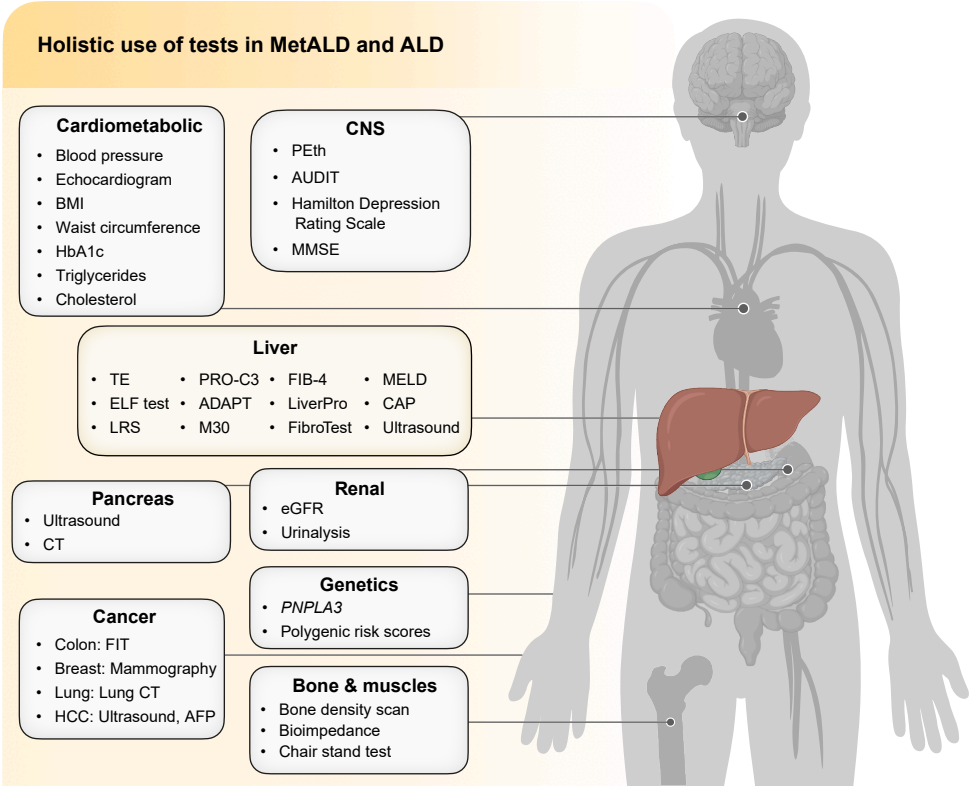

Fig. 2. Holistic approach to the management of patients with MetALD or ALD. The figure shows a range of tests that can be considered when diagnosing and treating a patient with ALD or MetALD. The use of tests should rely on an individual assessment and all suggested tests should not be used for all patients. AFP, alpha-fetoprotein; ALD, alcohol-related liver disease; AUDIT, alcohol use disorders identification test; CAP, controlled attenuation parameter; CNS, central nervous system; eGFR, estimated glomerular filtration rate; ELF, enhanced liver fibrosis; FIB-4, fibrosis-4; FIT, faecal immunochemical test; HbA1c, glycated haemoglobin; HCC, hepatocellular carcinoma; MetALD, metabolic and alcohol-related liver disease; PRO-C3, N-terminal type III collagen propeptide; TE, transient elastography.

Prognostic assessment and monitoring of disease progression

Establishing prognosis and the ability of NITs to monitor disease progression is crucial for patient management, including risk stratification and deciding on monitoring intervals. ALD progresses faster than MASLD and has a higher mortality rate than other aetiologies.[67,68] Alcohol intake is the primary risk factor for progression but the presence of metabolic syndrome in patients with ALD is also associated with higher mortality.[69] Meta-analyses show a close dose-response relationship between the amount of alcohol intake and risk of cirrhosis, with above two drinks per day for women and three drinks per day for men associated with increased risk.[70] In individuals with compensated cirrhosis, the cumulative 5-year risk of decompensation has been reported to be approximately 34% in patients with ALD.[71] Although data on the natural history of MetALD are currently limited, existing evidence suggests that its rate of progression falls between that of MASLD and ALD.[72–74] Following decompensation, the 1-year mortality rate for ALD-related cirrhosis can be as high as 34%.[75]

Louvet *et al.* concluded in a large cohort study of 650 patients with biopsy-proven compensated alcohol-related cirrhosis that no amount of alcohol consumption could be considered safe in patients with cirrhosis.[76] In this study, the majority of patients were previously decompensated, had discontinued intake of alcohol at baseline, and were followed every 6 months for close to 4 years. A third of patients relapsed, while patients with no alcohol consumption in the follow-up period had significantly better prognosis.[76] Further, in ALD cirrhosis, abstinence improved patients' prognosis with regard to decompensation and mortality across all stages of portal hypertension.[77]

Risk of progression to cirrhosis, decompensation and death

Several NITs including TE, ELF, FibroTest and FIB-4 were compared head-to-head with Kleiner fibrosis stage for their ability to predict liver-related events and death in a study of 462 patients with ALD over 4 years of follow-up.[78] All tests showed good C-statistics above 0.80 for prediction of liver-related events, with TE as the highest ranking with a C-statistic of 0.876. Interestingly, TE outperformed Kleiner fibrosis stage as a prognostic test. In patients with a TE value below 10 kPa, the 4-year risk of decompensation was minimal.[78] Among those with TE values between 10 and 15 kPa, 21% experienced a liver-related event during the follow-up period. This proportion increased to 54% in patients with a baseline TE above 15 kPa.[78] Further, PRO-C3 and ADAPT revealed good prognostic performances, with C-statistics of 0.80-0.81 (PRO-C3) and 0.81-0.85 (ADAPT) in the same cohort of patients from primary and secondary care settings.[79] In later stages of disease, recompensation in patients with ALD cirrhosis who maintained persistent alcohol abstinence resulted in a >90% decrease in liver-related deaths.[80]

The combination of genetic risk alleles into polygenic risk scores is a strategy for population-level risk stratification (Fig. 3).[81] Several polygenic risk scores have been developed to identify patients with a higher risk of ALD cirrhosis.[82–84] A genetic risk score including three single nucleotide polymorphisms (*PNPLA3*:rs738409, *SUGP1-TM6SF2*:rs10401969, *HSD17B13*:rs6834314) was developed in a case-control study of people with very high alcohol intake (≥80 g/day for men, ≥50 g/day for women).[83] The genetic risk score was used to separate patients into risk quintiles, and patients in the group with the highest risk had an odds ratio of 2.7-5 for ALD cirrhosis compared to low-risk individuals. Polygenic risk scores have been criticised for lacking adequate discriminative power for translation into clinical practice.[85] To address this, the potential added value of polygenic risk scores over accessible scores such as FIB-4 and APRI has been evaluated, but they have been shown to improve prognostic performance only minimally.[86]

Monitoring disease progression

New data are emerging on the use of dynamic changes in NITs to monitor disease progression or regression and improve risk stratification in ALD. A recent study included 371 patients with ALD and two LSMs taken a median of 25 months apart.[87] In the patients with compensated advanced chronic liver disease, those whose LSM increased by ≥20% had a four-fold higher risk of later decompensation than patients whose LSM decreased at the follow-up measurement, suggesting that TE is an effective tool for monitoring progression.[87] Similar results were observed in a cohort of over 2,500 patients of mixed aetiologies, where an increase in LSM correlated with a 50% higher risk of decompensation. Data suggested that dynamics in LSM were a better predictor of decompensation than dynamics in FIB-4 and MELD, or baseline LSM.[88]

Biomarkers for alcohol consumption

The development of the new nomenclature for SLD and the subgrouping of MASLD, MetALD, and ALD has nuanced the understanding of metabolic risk factors and alcohol intake as coexisting risks in a disease spectrum.[2,89] The MetALD subgroup acknowledges that patients often have both metabolic dysfunction and increased alcohol intake as drivers of disease progression, and these risk factors may synergistically contribute to progression.[2,90] This has further revitalised the discussion on the importance of assessing alcohol intake in these patients to allow for a better prognostic assessment, as misclassification as presumed MASLD is common.[91] In a Swedish epidemiological study of more than 15,000 patients with an ICD-diagnosis of MASLD, 12.2% of patients had a previous ALD or AUD diagnosis, which increased their risk of major adverse liver outcomes three-fold.[92] Further, in a study including 114 patients with presumed MASLD, measurements of ethyl glucuronide in hair revealed moderate to excessive alcohol intake in 29.8% within the last 3 months.[93] Interestingly, a study including 1,042 patients at risk of SLD assessed at baseline and after 2 years found the SLD classification to be highly dynamic, mostly due to changes in alcohol intake and hepatic steatosis.[94] For patients with MetALD or ALD, more than 60% had changed subclass after 2 years.[94]

In the SLD nomenclature, the differentiation between MASLD, MetALD, and ALD is based on patients' self-reported alcohol intake.[2] However, several different direct and indirect biomarkers for alcohol consumption measured from blood, urine, and hair are available, each with its own advantages and limitations.[95] Indirect biomarkers of alcohol intake included in routine blood tests, such as gamma-glutamyltransferase, AST,

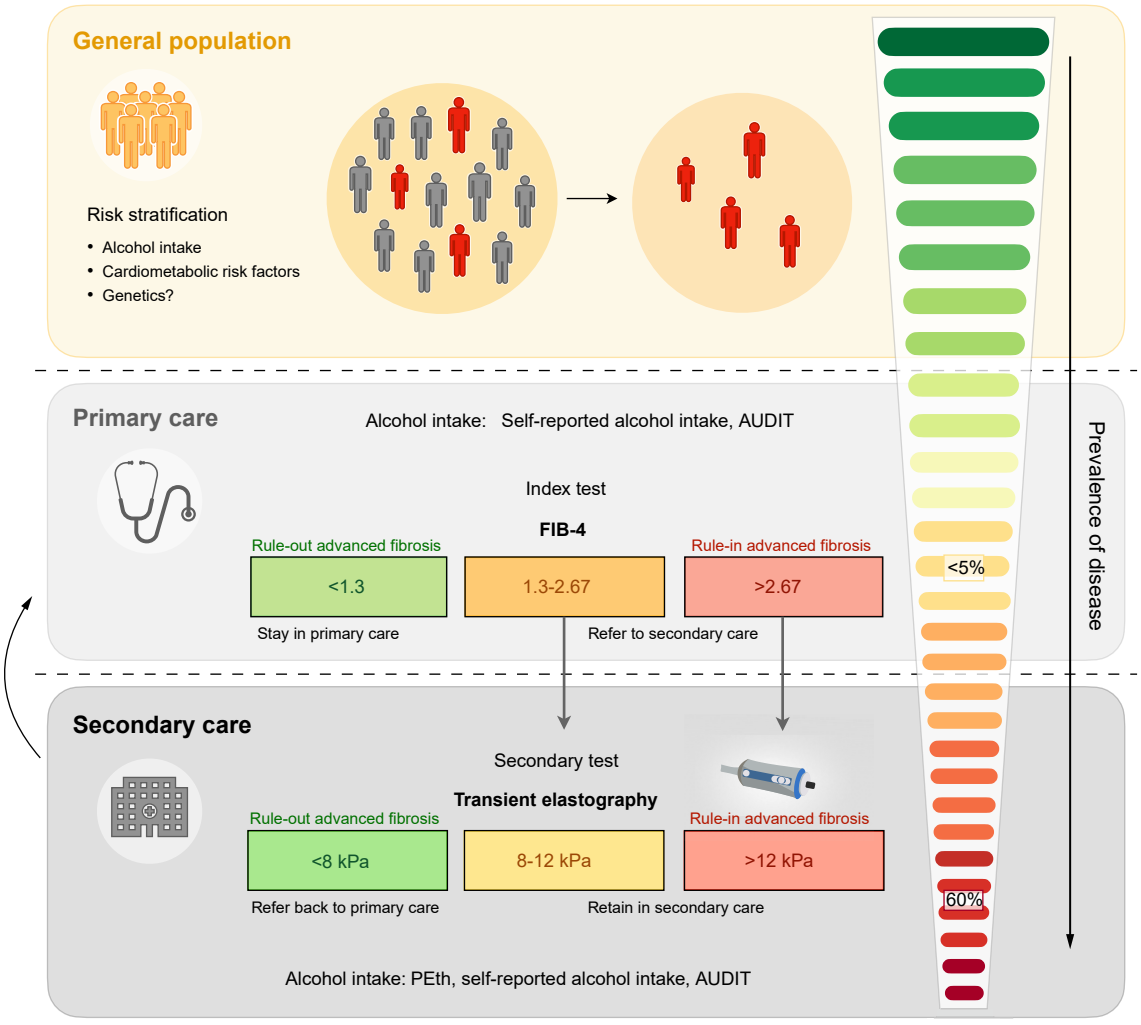

Fig. 3. Patient journey coupled with NITs. The figure illustrates the patient's journey from initial risk stratification within the general population, through the application of widely available and cost-effective NITs in primary care, to the use of more advanced NITs in secondary care. Tertiary care (not shown) often overlaps with secondary care in terms of the NITs used; however, additional NITs used at this stage are typically more specialised and guided by specific indicators of hepatic and multi-organ dysfunction, such as the MELD score and related clinical parameters.[124] In the figure, primary care is defined as the first point of contact in the healthcare system, typically provided by general practitioners, and secondary care refers to specialised medical care often upon referral from primary care. AUDIT, alcohol use disorders identification test; FIB-4, fibrosis-4; LRS, LiverRisk score; MELD, model for end-stage liver disease; MMSE, mini mental state examination; NITs, non-invasive tests; PEth, phosphatidylethanol.

ALT, and signs of macrocytic anaemia, are accessible and inexpensive, but their utility as markers of alcohol use is limited.[96]

While direct ethanol measurement, whether via breath or blood testing, is widely used to detect recent alcohol intake, *e.g.* in emergency departments or roadside settings, its utility as a clinical biomarker for ALD is limited.[96] Blood and breath ethanol levels reflect only short-term consumption and are influenced by factors such as time since last drink and sampling conditions. Consequently, they provide little information about chronic or hazardous drinking patterns, which are more clinically relevant in the context of liver disease. In clinical trials, ethanol testing may be used to verify recent abstinence, but it lacks the sensitivity and specificity needed for long-term monitoring. More reliable markers of sustained alcohol use include phosphatidylethanol (PEth), carbohydrate-deficient transferrin, and ethyl glucuronide (EtG).[95] In today's practice, testing for alcohol consumption is most commonly performed to ensure alcohol abstinence in patients on the waiting list for liver transplantation.[97] PEth can detect alcohol use for up to 2-4 weeks.[95] An international consensus has defined cut-offs for PEth concentrations reflecting alcohol intake, where a concentration <20 ng/ml is defined as indicative of low alcohol intake or abstinence, while concentrations ≥200 ng/ml strongly suggest chronic excessive alcohol intake.[98] In patients with chronic liver disease, PEth ≥80 ng/ml has identified patients drinking ≥4 drinks/day with a sensitivity of 91% and specificity of 77%.[99] Recent studies have shown varying results regarding the diagnostic accuracy of PEth. When PEth was recently compared to self-reported alcohol intake in 279 patients with chronic liver disease, big discrepancies between the two highlighted the need for objective measures.[100] Only in a third of patients did PEth levels and self-reporting align, and 57.7% of patients underreported their alcohol intake.[100] In 192

patients with MetALD/ALD included as part of randomised controlled trials, PEth was a stronger predictor of later decompensation and death than self-reported alcohol intake.[101] A study involving 116 individuals with alcohol-related cirrhosis evaluated PEth as a marker of recent alcohol intake by comparing it to self-reported intake using the timeline follow-back method.[102] The study found that PEth was a highly accurate biomarker for detecting alcohol use. Within a detection period of 3 weeks, PEth identified excessive alcohol use, defined as over 50 g/day for women and over 60 g/day for men, with 83% sensitivity and 81% specificity. For lower thresholds of increased intake (more than 20 g/day for women and 30 g/day for men), PEth achieved a sensitivity of 77% and a specificity of 90%.[102] Tavaglione *et al.* evaluated the diagnostic accuracy of PEth for subclassifying SLD in 374 individuals with overweight or obesity. PEth demonstrated good diagnostic performance for detecting MetALD, with an AUROC of 0.81.[103]

EtG can be detected in hair for up to a month and in urine for 3 days.[104] Urinary EtG testing in patients with liver disease, mainly cirrhosis of various aetiologies, showed a sensitivity of 76% and a specificity of 93% for detecting alcohol use within the past 3 days, using self-reported intake as the reference standard..[104]

The Alcohol Use Disorders Identification Test (AUDIT) is recommended to screen for harmful alcohol consumption. As a 10-question screening tool, it identifies patients with AUD (score >8) and alcohol dependence (score >20).[105] AUDIT-C, comprising the three alcohol consumption questions from AUDIT, is suggested as a quick, easy test.[106] Repeated assessment of AUDIT-C was used as an estimate of alcohol intake in a recent study including 1.1 million patients with SLD.[107] Patients stratified as having high-risk alcohol use had a 43% higher risk of later cirrhosis compared to abstinent patients, while a decrease from high-risk use in the follow-up period resulted in a 39% reduction in cirrhosis risk.[107]

Novel biomarkers for precision management

The rapid evolution of omics-based technologies promises an emerging shift towards precision medicine. Methods to generate several types of omics data are rapidly decreasing in cost and increasing in speed and depth. These powerful, innovative technologies will most certainly lead to a vast number of novel biomarkers at various molecular levels, including genomics, transcriptomics, proteomics, metabolomics, lipidomics, and the microbiome, to enhance disease diagnosis, prognosis, and therapeutic strategies. However, while omics-based biomarker discovery shows great potential, it is still in an exploratory phase in hepatology.[108] Some key limitations also hinder widespread use, such as a lack of standardisation, generalisability, and validation across diverse, independent cohorts.

The most promising study so far within omics-based biomarker discovery in ALD was by Niu *et al.* on mass spectrometry proteomics.[109] In this study, which included 459 patients with biopsy-controlled ALD and 137 healthy controls, machine learning models identified biomarker panels with an AUROC of 0.92 for detecting significant fibrosis (≥F2), with performance equal to TE. The proteomics biomarker panel was also an accurate prognostic test, with a C-statistic of 0.90 for predicting liver-related events.

Lipidomics provides important information on bioactive lipids and lipotoxicity in ALD. For example, two independent studies showed that lower levels of sphingomyelin SM(d41:1) correlated with higher fibrosis stage, and predicted liver-related events and both short- and long-term mortality in patients with ALD across the spectrum of disease.[110,111]

Future directions

ALD and MetALD are leading causes of morbidity, mortality, and liver transplantation for patients with SLD. However, we are now entering a transformative era in understanding and managing the spectrum of SLD, fuelled by advances in clinical research and a growing appreciation of the interplay between alcohol and metabolic dysfunction.[3,112]

The therapeutic landscape is also rapidly evolving. Two pivotal phase II clinical trials within the ALD/MetALD spectrum, conducted by Novo Nordisk and GSK, are eagerly anticipated and could provide valuable insights into pharmacological interventions for this dual-hit phenotype.[22,23] Simultaneously, the maturation of non-invasive diagnostic technologies, validated extensively in ALD and MetALD, has enabled early detection, with diagnostic cut-offs harmonised with those established for metabolic dysfunction-associated steatohepatitis. These tools, together with growing evidence from trials like GALA-RIF, demonstrate the feasibility of randomised trials in this population, with high participant compliance, including in trials involving invasive procedures.[113]

Significant progress has been made in pharmacotherapy, exemplified by the recent phase III ESSENCE trial of semaglutide. This study demonstrated not only reversal of inflammation but also a significant impact on fibrosis, with an absolute risk reduction of 14.4%, heralding a paradigm shift in treatment expectations. Given the well-established safety and efficacy of GLP-1 receptor agonists, further exploration of dual and triple agonists holds promise for even greater efficacy.[114–116] Observational data consistently show that GLP-1 analogues reduce the risk of recurrent alcohol-related hospitalisations, underscoring their potential in this dual-pathway disease.[117]

Additionally, experimental and clinical evidence suggests that fibroblast growth factor 21 analogues may offer dual benefits in ALD, with antifibrotic effects peripherally and reductions in alcohol consumption centrally.[118–123] These mechanisms align with the growing body of preclinical data and provide a strong rationale for ongoing trials in this area.

In conclusion, the convergence of advances in nomenclature, diagnostics, and therapeutics is set to redefine the management of ALD and MetALD. The emergence of effective pharmacological interventions, coupled with enhanced capabilities for early detection and prevention, offers a transformative opportunity to change the trajectory of disease progression across the spectrum of SLD. This emerging landscape fuels optimism for improved patient outcomes and underscores the necessity of continued investment in research and innovation in this field.

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Abbreviations

ALD, alcohol-related liver disease; ALT, alanine aminotransferase; APRI, aspartate aminotransferase-to-platelet-ratio index; AST, aspartate aminotransferase; AUD, alcohol use disorder; AUDIT, alcohol use disorders identification test; ELF test, enhanced liver fibrosis test; EtG, ethyl glucuronide; FIB-4, fibrosis-4; LSM, liver stiffness measurement; MASLD, metabolic dysfunction-associated steatotic liver disease; MELD, model for end-stage liver disease; MetALD, metabolic and alcohol-related liver disease; NIT, non-invasive test; PEth, phosphatidylethanol; PRO-C3, N-terminal type III collagen propeptide; SLD, steatotic liver disease; TE, transient elastography.

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Conflicts of interest

MT: speaker fees from Echosens, Madrigal, Siemens Healthcare, Norgine, Takeda, and Tillotts Pharma, and advisory fees from Boehringer Ingelheim, GSK, Novo Nordisk, AstraZeneca. Co-founder and board member of Evido. AK has served as speaker for Novo Nordisk and Norgine and participated in advisory boards for GSK, Boehringer Ingelheim and Novo Nordisk, all outside the submitted work. Research support; Norgine, Siemens, Nordic Bioscience, Astra, Echosense. Board member and co-founder Evido. SJ reports no conflicts of interest.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Conceptualization: SJ, AK. Writing – original draft: SJ, AK. Writing – review and editing: SJ, MT, AK. Visualization: SJ, AK. Supervision: MT, AK. Funding acquisition: MT, AK.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used AI (ChatGTP version 4 and 4o) in order to improve language and readability. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Supplementary data

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